Remarks

I. Introduction

Claims 17-30 and 46-58 remain pending in this application. New claims 59-71 are directed to a method for reducing the desire to drink alcohol and have been added in the interest of advancing prosecution of the application. Support for claims 59-71 is found in the specification, particularly at paragraph 81 of the published application. No new matter is introduced in these claims. Applicant respectfully requests that the Examiner consider the below remarks and allow the pending claims.

II. Interview with Examiner

Applicant would like to thank Examiner Jennifer Kim and her supervisor, Examiner Sreenivasan Padmanabhan, for their time and consideration during the interview with Applicant's representatives on October 24, 2006. During the interview, the primary differences between withdrawal and dependency, as well as the claimed timing and dosage ranges were discussed.

III. 35 U.S.C. §103

- **Gerra and Nutt references**

Claims 17-26, 29, 31-40, 43 and 45 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Gerra et al. (*Current Therapeutic Research*, 1991, hereinafter Gerra) in view of Nutt et al. (*Alcohol and Alcoholism*, 1993, hereinafter Nutt). Applicant respectfully traverses this rejection and requests reconsideration and withdrawal thereof.

Applicant's representative respectfully asserts that Gerra and Nutt are concerned with treating alcohol withdrawal symptoms. Gerra and Nutt, considered alone or together do not

in any way disclose, suggest or provide motivation to one of ordinary skill in the art to treat alcohol dependency with flumazenil. Further, Gerra and Nutt, alone or together do not in any way disclose, suggest or provide motivation to one of ordinary skill in the art to administer flumazenil in order to reduce the desire to drink alcohol. These references, considered alone or together, further do not in any way disclose, suggest or provide motivation to one of ordinary skill in the art to administer flumazenil in the claimed dosing regimen for any purpose, including administration to reduce the desire to drink alcohol or to treat alcohol dependency. There is no scientific or medical rationale provided in the Office Action to support the assertion that Gerra and Nutt would lead one of ordinary skill to derive Applicant's claimed method. The Examiner states on page 11, last paragraph, "Gerra et al. and Nutt et al. do not teach the reduction or elimination of the desire to drink alcohol by flumazenil". Accordingly, Applicant's claims are not rendered obvious by the combination of these references, particularly the claims reciting administration of flumazenil to reduce the desire to drink alcohol.

Because the Examiner's supervisor indicated that treating withdrawal would inherently treat dependency, Applicant has addressed that assertion in part A below, even though it was not expressly discussed in the pending Office action. Additionally, without acquiescing to the inherency arguments, Applicant continues to maintain that the claimed dosing regimen is not taught or suggested by the prior art, as discussed below in part B.

A. Withdrawal vs. dependency (and why treating withdrawal does not inherently treat dependency)

In response to Applicant's previous arguments about the distinction between alcohol withdrawal vs. alcohol dependency, the Examiner's position is that "Gerra clearly teaches treatment of the ethanol addicts with dependency" by administering flumazenil. However, the Gerra and Nutt methods are directed toward treating alcohol *withdrawal symptoms* – not treating alcohol *dependency*. Gerra and Nutt do not mention, hint, suggest or provide motivation for a skilled artisan to administer flumazenil in order to treat alcohol dependency or to reduce the cravings or desire to drink alcohol, as claimed. One of ordinary skill could not read Gerra and Nutt together and derive Applicant's claimed method.

As previously argued, dependency develops over time. Even when withdrawal symptoms are treated, dependency can persist, as outlined in the below chart. By contrast, alcohol withdrawal symptoms (e.g., elevated temperature, increased blood pressure, rapid heart rate, restlessness, psychosis, seizures) are experienced over a short period of time. Even if withdrawal symptoms are treated and subside, an individual may still be "dependent" upon alcohol. That is where the Gerra and Nutt references stop short. Simply stated, treating alcohol withdrawal symptoms is different from treating alcohol dependency and is also different from administering flumazenil in order to reduce the desire or cravings to drink alcohol.

Withdrawal	Dependency
Evaluated with CIWA[1] score: Symptoms: • seizures • delirium tremens • weakness • sweats • nausea • depression • insomnia	Evaluated using DSM IV[2] criteria: Symptoms: • impaired judgment • impaired control over drug use • tolerance • withdrawal upon abstaining • imbibe more than intended • unsuccessful efforts to stop • taken to avoid withdrawal • time spent in obtaining the substance replaces social, occupational or recreational activities • continued use despite adverse consequences
Short term (1-2 days)	Long term (weeks to years)
Reduction of withdrawal symptoms does not cause abstinence or reduction in cravings	Reduction in dependency causes reduction in use, abstinence, reduction in desire for use of substance, cravings, anxiety

If the Examiner argues that treating withdrawal symptoms would *inherently* treat dependency, that position would be incorrect. If a person is not experiencing acute withdrawal symptoms, but nonetheless remains dependent upon alcohol, neither of the cited references, alone or in combination, teaches or provides motivation to treat that alcohol-dependent patient with flumazenil (and specifically not with the claimed dosing regimen as discussed below). In other words, treating the withdrawal symptoms does not necessarily treat the cravings associated with dependency or reduce the desire to drink alcohol. Thus, administering flumazenil to treat alcohol dependency and to reduce the desire to drink alcohol does not "necessarily follow" from treating withdrawal symptoms as described by Gerra and Nutt.

[1] J Clin Psychopharmacol, 1981, 1:382-387.
[2] DSM-IV, American Psychiatric Association, Washington D.C., 1994.

Inherency is only found when the invention "necessarily follows" or is a "natural result following from" practicing a process described in a prior art reference. A case with analogous facts is Rapoport v. Dement, 254 F.3d 1053 (Fed.Cir. 2001). In Rapoport, the court addressed the patentability of a claim for "a method for the treatment of sleep apnea", which was formulated in the course of an interference proceeding. The relevant part of the claim at issue provides:

1. A method for treatment of sleep apneas comprising administration of a therapeutically effective regimen of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment....

The Board of Appeals declared Dement to be the senior party and, in response, Rapoport filed a motion claiming that a prior art publication, authored by Rapoport, rendered the claims anticipated and/or obvious. At issue, then, was whether Rapoport's publication (the "FPR Publication") disclosed the claimed method.

Among other arguments, Rapoport asserted that the FPR Publication disclosed a method of treating a secondary symptom related to sleep apnea, anxiety, using buspirone, which all parties agreed is within the definition of a "Formula I azapirone compound". Therefore, according to Rapoport, the FPR Publication discloses the administration of a therapeutically effective regimen of Formula I azapirone compound (buspirone) in a manner that would inherently treat sleep apnea and, thus, the claim is anticipated.

The Federal Circuit clearly rejected this argument and deemed it "without merit". See Id. at 1062. For the FPR Publication's disclosure to be anticipating, one must assume that a person would have used the buspirone in the precise manner required to actually treat sleep

apnea (as opposed to anxiety), even though that specific administration protocol, and the objective of treating sleep apnea, was never disclosed in the FPR Publication. Treating anxiety, even though related to sleep apnea, is simply not the same as treating sleep apnea and, therefore, a publication that discloses the use of a drug to treat anxiety cannot anticipate the use of that same drug to treat sleep apnea. The Federal Circuit concluded "[i]nherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. at 1063 (citing Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed.Cir.1991)). See also *Glaxo Group v. Teva Pham. USA, Inc.*, No. CIV.A.02-219 GMS, 2004 WL 1875017, at *18-20 ("Although inherent anticipation does not require the element to be present each and every time, it does require the result to be a necessary and inevitable consequence of practicing the invention claimed in the prior art under normal conditions." Glaxo, 2004 WL 1875017, at *19. (emphasis added)).

In the present case, treating alcohol withdrawal symptoms with flumazenil does not inherently anticipate treating the cravings or desire to drink alcohol or treating alcohol dependency. Following cessation of withdrawal symptoms, the cravings or desire to drink in alcohol dependent individuals persist. Accordingly, a reduction in the cravings or desire to drink alcohol is not a necessary and inevitable consequence of the use of flumazenil to treat withdrawal symptoms. As in Rapoport, it is without merit to claim that treating alcohol withdrawal symptoms, particularly using an administration protocol not disclosed in the prior art, can anticipate a treatment for alcohol dependency or a treatment for dependency that reduces a patient's desire to drink alcohol.

Treatment of alcohol withdrawal symptoms is recognized by those of ordinary skill in the art as different from treatment of alcohol dependence. Exhibit A is an article by Bayard et al., (American Family Physician 2004 :69:1443-1450) which clearly indicates on page 1443 (Abstract) and on 1448, second column, fourth paragraph, that

> "Treatment of alcohol withdrawal syndrome should be followed by treatment for alcohol dependence. Treatment of withdrawal alone does not address the underlying disease of addiction and therefore offers little hope for long-term abstinence."

Bayard et al., clearly indicates that treatment of alcohol withdrawal symptoms is recognized as different from treatment of alcohol dependence. There is no support in the Office Action for the assumption that these treatment methods are equivalent. In fact, the art (Bayard et al.) indicates these treatments are different and not equivalent. For at least these reasons, Applicant asserts that the rejection in view of Gerra and Nutt under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

B. The cited references do not teach or suggest the claimed dosing regimen

Furthermore, the dosage regimens described by the prior art are either a two-day process (Gerra) or a one-minute bolus dose (Nutt). Neither reference, alone or in combination, teaches, suggests or provides motivation to use a smaller amount of flumazenil administered sequentially over 1 to 15 minutes for any purpose. As discussed above, neither reference, alone or in combination, teaches, suggests or provides motivation to use flumazenil to reduce the cravings and desire to drink alcohol, or to treat alcohol dependency.

- Gerra - doses of 0.5 mg every six hours for 48 hours (for a total of 2 mg/day)
- Nutt – a dose of 2 mg over 1 minute (for a total of 2 mg/day)

The regimens of the prior art were designed in order to measure the effects of flumazenil on withdrawal – i.e., the acute symptoms of elevated temperature, increased blood pressure, rapid heart rate, restlessness, psychosis, and seizures. In fact, the effects of flumazenil reported by Nutt were quite variable, in most patients causing increased sweating and anxiety (page 337, Abstract; page 339, 2nd full paragraph). In some of Nutt's patients withdrawal symptoms disappeared and then returned (page 339, 3rd full paragraph). Accordingly, the cited art does not prove efficacy in treatment of withdrawal symptoms. The Examiner's position is that it would have been obvious to optimize the time intervals and divide portions of known daily effective doses of 2 mg/day, although these doses were not effective and the results were variable as discussed in this paragraph. However, the Examiner fails to describe where that motivation comes from, other than stating that "[o]ne would have been motivated to optimize the dosing intervals and optimize the daily amounts in portions to achieve an ultimate therapeutic regimen needed for individual patient's medical requirements." This assertion does not describe why one would be motivated to change Gerra, which divides a 2 mg/day dosage of flumazenil over two 24-hour periods, or Nutt, which administers a single dose of 2 mg in one minute. Simply put, neither reference, alone or in combination, teaches or suggests any benefit to changing their dosing regimen in order to arrive at sequentially administering flumazenil in doses of between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes. The Examiner has not stated any scientific or medical rationale why a skilled artisan would seek to modify these

ranges, specifically considering that the Gerra and Nutt references are directed toward evaluating the efficacy of flumazenil on withdrawal symptoms (a different objective), not treating alcohol dependency, or decreasing the cravings and desire to drink alcohol. There is simply no teaching, suggestion or motivation in the cited references that would lead one to experiment with sequential low doses of flumazenil more often that taught by the art to arrive at different administration dosages and timing intervals to treat a different condition or to reduce the desire to drink alcohol.

In view of the preceding arguments, the claimed methods of treating alcohol dependency and/or reducing the desire to drink alcohol, are not obvious in view of Gerra and Nutt. These references – whether take alone or in combination – fail to teach, suggest or provide motivation to derive Applicant's claimed method. In fact, absent the teachings of the present specification, one of ordinary skill would fail to arrive at the claimed methods, and as the Examiner knows, using that kind of hindsight is impermissible. For at least these reasons, Applicant asserts that the rejection in view of Gerra and Nutt under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

- **Opitz patent**

Claims 27-28, 41, and 42 have been rejected as being unpatentable over the combination of Gerra and Nutt, in view of U.S. Patent No. 5,519,017 to Opitz. The Examiner acknowledges that Gerra and Nutt do not teach the specific additional agents such

as clomethiazole (claims 27, 41[3]), piracetam, and disulfiram (claims 28, 42[4]), but submits that Opitz teaches that the drugs can be used to control the influence of alcohol (with clomethiazole used for alcoholic delirium, piracetam used for palliatives or acute alcohol withdrawal, and disulfiram used for treatment of alcoholism). Applicant respectfully traverses this rejection and requests reconsideration and withdrawal thereof.

First, the Opitz disclosure does not make up for the deficiencies of Gerra and Nutt in treating alcohol dependency with flumazenil or reducing the desire to drink alcohol, and thus fails to render the claimed methods obvious. In addition, with respect to the new claims presented in this response, Opitz teaches away from using disulfiram to reduce the desire to drink alcohol. *See* col. 1, lines 50-55, which states that disulfiram (Antabus®) does not "reduce the strong desire for alcohol". This is additional support for the patentability of new claim 70. For at least these reasons, Applicant asserts that the rejection in view of Gerra and Nutt in view of Opitz under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

- **Aguirre reference**

Claims 30 and 44 are rejected as being unpatentable over the combination of Gerra and Nutt, in view of Aguirre et al. (*Alcohol*, 1990). The Examiner acknowledges that Gerra and Nutt do not teach the reduction or elimination of the desire to drink alcohol by delivering flumazenil (page 11, last paragraph of the Office Action). However, the Examiner asserts that Aguirre teaches that the decreased levels of β-endorphin cause chronic alcohol

[3] Claim 41 has been cancelled, but we expect that the Examiner intended to reject claim 56.
[4] Claim 42 has been cancelled, but we expect that the Examiner intended to reject claim 57.

consumption (Office Action at page 12, lines 1-2, 6-7), and Gerra teaches that flumazenil significantly raises the plasma concentration of β-endorphin (cited by the Examiner at page 11, fourth paragraph, referring to Gerra at page 65, lines 32-35). The Examiner submits that it would have been obvious to "...employ flumazenil as taught by Gerra et al. as modified by Nutt et al. for the treatment of alcohol dependency to reduce the alcohol consumption in order to achieve an expected benefit of flumazenil's effectiveness in eliminating the cause of alcohol consumption by increasing β-endorphin levels in alcoholics" (page 12, lines 7-11). Applicant respectfully traverses this rejection and requests reconsideration and withdrawal thereof.

The Examiner's conclusion appears based on the assumption that <u>because</u> β-endorphin levels are decreased in alcoholics, raising β-endorphin levels treats dependency. This logic implies that a decrease in β-endorphin levels causes alcoholism and that increasing β-endorphin levels in alcoholics <u>will</u> reduce dependency on alcohol. A simple observation that β-endorphin levels are lower in alcoholics in no way implies that increasing β-endorphin levels would eliminate the cause of alcohol consumption. No scientific or medical justification is provided for the Examiner's assertion. An observation concerning a change in one biological marker appears to be the basis for speculating that reversing the change will cure a disease such as alcohol dependency. Many diseases and conditions cause a change in a biological marker, however this does not mean to one of ordinary skill in the art that reversing the levels of the biological marker inherently treats a disease. For example, cancer patients often have increased blood coagulation, however administration of blood thinners does not treat cancer.

Aguirre merely speculates on multiple causes and effects for the results found – it speculates ("a possibility") that low β-endorphin levels may be a cause of alcoholism or a "biological alcoholism marker" (see page 410, 2nd column, last paragraph – page 411, 1st column, lines 3-6). In fact, Aguirre measured plasma levels of β-endorphin that were lower in alcoholics abstaining from alcohol than levels in patients currently ingesting alcohol (page 410, second column). Thus, Aguirre does not definitively indicate that a decrease in β-endorphin levels is necessarily *caused* by alcoholism. To imply anything further from Aguirre is an unwarranted extrapolation of this reference.

Further, Gerra, on page 65, reference 17, refers to an abstract reporting the analgesic effects of flumazenil in cancer patients with pain (see also reference #17 on page 66). Cancer patients, especially those in pain, are a different patient population than alcohol dependent patients. Pain has effects on the opioid system as well known in the art. No additional details are available concerning this abstract and the abstract was not provided by with the Office Action. Gerra describes endogenous opioids as "possible mediators" of flumazenil's action in alcohol withdrawal (page 65 fourth paragraph). Gerra does not address alcohol dependency or use of flumazenil to reduce the desire to drink alcohol.

As discussed above, Gerra and Nutt do not address treatment of alcohol dependency or use of flumazenil to reduce the desire to drink alcohol. For at least this reason, Aguirre does not cure the deficiencies of Gerra and Nutt. Further, nothing in the combination of Gerra, Nutt and Aguirre, provides any indication that increasing β-endorphin levels may be useful for treating alcohol dependency or reducing the desire to drink alcohol, as claimed.

Applicant submits that one of ordinary skill in the art would not be motivated to combine the teachings of Gerra, either as the primary reference or in the Japanese abstract concerning analgesic effects of flumazenil in cancer patients, with Aguirre and Nutt, to derive Applicant's invention, as claimed. Without using the impermissible hindsight provided by Applicant's teachings, the combination of Gerra, Nutt, and Aguirre would not provide one of ordinary skill in the art with a reasonable expectation that flumazenil, at the claimed dosages, would be an effective drug to reduce the desire to drink alcohol or treat alcohol dependency. None of the cited references, alone or together, provide a suggestion that flumazenil would reduce the desire to drink alcohol or treat alcohol dependency. Accordingly, Applicant respectfully asserts the rejection in view of Gerra and Nutt and further in view of Aguirre under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

Claims 56 and 57 are rejected under 35 U.S.C. §103(a) as obvious over Gerra in view of Nutt, further in view of Aguirre and further in view of Opitz. Applicant's arguments have already addressed the combination of Gerra and Nutt, and the further combination of Gerra and Nutt with Opitz or with Aguirre (as applied to claims 30, 46-55 and 58). For at least the reasons provided above, Applicant respectfully asserts that none of these combinations of references renders obvious the claimed invention. Applicant requests withdrawal of the rejection of claims 56 and 57 under 35 U.S.C. §103(a).

IV. Double Patenting

The provisional rejection of claims 17-45 on the ground of non-statutory obviousness-type double patenting over claims 1, 3-6, 8-13 and 28 of co-pending application serial

number 11/111,435 is maintained. Applicant respectfully re-requests deferral of this rejection until such time that allowable subject matter is found in both applications.

Conclusion

For at least the above reasons, Applicant respectfully requests allowance of the pending claims and issuance of a patent in due course. If there remain any additional issues to be addressed, the Examiner is invited to contact the undersigned at 404.745.2470.

Respectfully submitted,

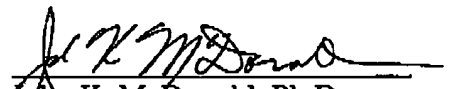

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EXHIBIT A

Alcohol Withdrawal Syndrome

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The spectrum of alcohol withdrawal symptoms ranges from such minor symptoms as insomnia and tremulousness to severe complications such as withdrawal seizures and delirium tremens. Although the history and physical examination usually are sufficient to diagnose alcohol withdrawal syndrome, other conditions may present with similar symptoms. Most patients undergoing alcohol withdrawal can be treated safely and effectively as outpatients. Pharmacologic treatment involves the use of medications that are cross-tolerant with alcohol. Benzodiazepines, the agents of choice, may be administered on a fixed or symptom-triggered schedule. Carbamazepine is an appropriate alternative to a benzodiazepine in the outpatient treatment of patients with mild to moderate alcohol withdrawal symptoms. Medications such as haloperidol, beta blockers, clonidine, and phenytoin may be used as adjuncts to a benzodiazepine in the treatment of complications of withdrawal. Treatment of alcohol withdrawal should be followed by treatment for alcohol dependence. (Am Fam Physician 2004;69:1443-50. Copyright© 2004 American Academy of Family Physicians)

In 1992, approximately 13.8 million Americans (7.4 percent of the U.S. adult population)[1] met the criteria for alcohol abuse or dependence as specified in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR).[2] In 2000, 226,000 patients were discharged from short-stay hospitals (excluding Veteran's Affairs and other federal hospitals) with one of the following diagnoses: alcohol withdrawal *(Table 1)*,[2] alcohol withdrawal delirium, or alcohol withdrawal hallucinosis.[3] It is estimated that only 10 to 20 percent of patients undergoing alcohol withdrawal are treated as inpatients,[4] so it is possible that as many as 2 million Americans may experience symptoms of alcohol withdrawal conditions each year.

Pathophysiology

Alcohol withdrawal syndrome is mediated by a variety of mechanisms. The brain maintains neurochemical balance through inhibitory and excitatory neurotransmitters. The main inhibitory neurotransmitter is γ-aminobutyric acid (GABA), which acts through the GABA-alpha (GABA-A) neuroreceptor. One of the major excitatory neurotransmitters is glutamate, which acts through the *N*-methyl-D-aspartate (NMDA) neuroreceptor.

Alcohol enhances the effect of GABA on

See page 1339 for definitions of strength-of-recommendation labels.

TABLE 1
Diagnostic Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 beats per minute)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Adapted with permission from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed., text revision. Washington, D.C.: American Psychiatric Association, 2000:216.

GABA-A neuroreceptors, resulting in decreased overall brain excitability. Chronic exposure to alcohol results in a compensatory decrease of GABA-A neuroreceptor response to GABA, evidenced by increasing tolerance of the effects of alcohol.

Alcohol inhibits NMDA neuroreceptors, and chronic alcohol exposure results in up-regulation of these receptors. Abrupt cessation of alcohol exposure results in brain hyperexcitability, because receptors previously inhibited by alcohol are no longer inhibited. Brain hyperexcitability manifests clinically as anxiety, irritability, agitation, and tremors. Severe manifestations include alcohol withdrawal seizures and delirium tremens.

An important concept in both alcohol craving and alcohol withdrawal is the "kindling" phenomenon; the term refers to long-term changes that occur in neurons after repeated detoxifications. Recurrent detoxifications are postulated to increase obsessive thoughts or alcohol craving.[5] Kindling explains the observation that subsequent episodes of alcohol withdrawal tend to progressively worsen.

Although the significance of kindling in alcohol withdrawal is debated, this phenomenon may be important in the selection of medications to treat withdrawal. If certain medications decrease the kindling effect, they may become preferred agents.

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Withdrawal Symptoms

The spectrum of withdrawal symptoms and the time range for the appearance of these symptoms after cessation of alcohol use are listed in *Table 2*. Generally, the symptoms of alcohol withdrawal relate proportionately to the amount of alcoholic intake and the duration of a patient's recent drinking habit. Most patients have a similar spectrum of symptoms with each episode of alcohol withdrawal.

Minor withdrawal symptoms can occur while the patient still has a measurable blood alcohol level. These symptoms may include insomnia, mild anxiety, and tremulousness. Patients with alcoholic hallucinosis experience visual, auditory, or tactile hallucinations but otherwise have a clear sensorium.

Withdrawal seizures are more common in patients who have a history of multiple episodes of detoxification. Causes other than alcohol withdrawal should be considered if seizures are focal, if there is no definite history of recent abstinence from drinking, if seizures occur more than 48 hours after the patient's last drink, or if the patient has a history of fever or trauma.

Alcohol withdrawal delirium, or delirium tremens, is characterized by clouding of consciousness and delirium. Episodes of delirium tremens have a mortality rate of 1 to 5 percent.[6] Risk factors for developing alcohol withdrawal delirium include concurrent acute medical illness, daily heavy alcohol use, history of delirium tremens or withdrawal seizures, older age, abnormal liver function, and more severe withdrawal symptoms on presentation.

Evaluation of the Patient in Alcohol Withdrawal

The history and physical examination establish the diagnosis and severity of alcohol withdrawal. Important historical data include quantity of alcoholic intake, duration of alcohol use, time since last drink, previous alcohol withdrawals, presence of concurrent medical or psychiatric conditions, and abuse of other agents. In addition to identifying withdrawal symptoms, the physical examination should assess possible complicating

TABLE 2
Symptoms of Alcohol Withdrawal Syndrome

Symptoms	*Time of appearance after cessation of alcohol use*
Minor withdrawal symptoms: insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia	6 to 12 hours
Alcoholic hallucinosis: visual, auditory, or tactile hallucinations	12 to 24 hours*
Withdrawal seizures: generalized tonic-clonic seizures	24 to 48 hours†
Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 to 72 hours‡

*—*Symptoms generally resolve within 48 hours.*
†—*Symptoms reported as early as two hours after cessation.*
‡—*Symptoms peak at five days.*

medical conditions, including arrhythmias, congestive heart failure, coronary artery disease, gastrointestinal bleeding, infections, liver disease, nervous system impairment, and pancreatitis. Basic laboratory investigations include a complete blood count, liver function tests, a urine drug screen, and determination of blood alcohol and electrolyte levels.

The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a validated 10-item assessment tool that can be used to quantify the severity of alcohol withdrawal syndrome, and to monitor and medicate patients going through withdrawal[7,8] *(Figure 1)*.[7] CIWA-Ar scores of 8 points or fewer correspond to mild withdrawal, scores of 9 to 15 points correspond to moderate withdrawal, and scores of greater than 15 points correspond to severe withdrawal symptoms and an increased risk of delirium tremens and seizures.

In using the CIWA-Ar, the clinical picture should be considered because medical and psychiatric conditions may mimic alcohol withdrawal symptoms. In addition, certain medications (e.g., beta blockers) may blunt the manifestation of these symptoms.

Differential Diagnosis

Alcohol withdrawal syndrome can be confused with other conditions. Thyrotoxicosis, anticholinergic drug poisoning, and amphetamine or cocaine use can result in signs of increased sympathetic activity and altered mental status. Central nervous system infection or hemorrhage can cause seizures and mental status changes. Withdrawal from other sedative-hypnotic agents causes symptoms similar to those occurring in alcohol withdrawal syndrome.

Goals of Treatment

The American Society of Addiction Medicine lists three immediate goals for detoxification of alcohol and other substances: (1) "to provide a safe withdrawal from the drug(s) of dependence and enable the patient to become drug-free"; (2) "to provide a withdrawal that is humane and thus protects the patient's dignity"; and (3) "to prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs."[6]

General Care

Abnormalities in fluid levels, electrolyte levels, or nutrition should be corrected. Intravenous fluids may be necessary in patients with severe withdrawal because of excessive fluid loss through hyperthermia, sweating, and vomiting. Intravenous fluids should not be administered routinely in patients with less severe withdrawal, because these patients may become overhydrated.

Routine administration of magnesium sulfate has not been shown to improve withdrawal symptoms,[9] but supplementation is appropriate if a patient is hypomagnesemic. Multivitamins and thiamine (100 mg per day) should be provided during treatment for alcohol withdrawal. If intravenous fluids are administered, thiamine (100 mg intravenously) should be given before glucose is administered, to prevent precipitation of Wernicke's encephalopathy.

Medication Regimens

Medication can be administered using fixed-schedule or symptom-triggered regimens *(Table 3)*.[10] With a fixed-schedule regimen, doses of a benzodiazepine are admin-

Assessment of Alcohol Withdrawal

Patient: _____ Date: _____ Time: ____:____

Pulse or heart rate, taken for one minute: _____ Blood pressure: ____/____

Nausea and vomiting. Ask "Do you feel sick to your stomach? Have you vomited?"
Observation:
0—No nausea and no vomiting
1—Mild nausea with no vomiting
2—
3—
4—Intermittent nausea with dry heaves
5—
6—
7—Constant nausea, frequent dry heaves, and vomiting

Tremor. Ask patient to extend arms and spread fingers apart.
Observation:
0—No tremor
1—Tremor not visible but can be felt, fingertip to fingertip
2—
3—
4—Moderate tremor with arms extended
5—
6—
7—Severe tremor, even with arms not extended

Paroxysmal sweats
Observation:
0—No sweat visible
1—Barely perceptible sweating; palms moist
2—
3—
4—Beads of sweat obvious on forehead
5—
6—
7—Drenching sweats

Anxiety. Ask "Do you feel nervous?"
Observation:
0—No anxiety (at ease)
1—Mildly anxious
2—
3—
4—Moderately anxious or guarded, so anxiety is inferred
5—
6—
7—Equivalent to acute panic states as occur in severe delirium or acute schizophrenic reactions

Agitation
Observation:
0—Normal activity
1—Somewhat more than normal activity
2—
3—
4—Moderately fidgety and restless
5—
6—
7—Paces back and forth during most of the interview or constantly thrashes about

Tactile disturbances. Ask "Do you have any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"
Observation:
0—None
1—Very mild itching, pins-and-needles sensation, burning, or numbness
2—Mild itching, pins-and-needles sensation, burning, or numbness
3—Moderate itching, pins-and-needles sensation, burning, or numbness
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Auditory disturbances. Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
Observation:
0—Not present
1—Very mild harshness or ability to frighten
2—Mild harshness or ability to frighten
3—Moderate harshness or ability to frighten
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Visual disturbances. Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
Observation:
0—Not present
1—Very mild sensitivity
2—Mild sensitivity
3—Moderate sensitivity
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

Headache, fullness in head. Ask "Does your head feel different? Does it feel like there is a band around your head?"
Do not rate for dizziness or lightheadness; otherwise, rate severity.
0—Not present
1—Very mild
2—Mild
3—Moderate
4—Moderately severe
5—Severe
6—Very severe
7—Extremely severe

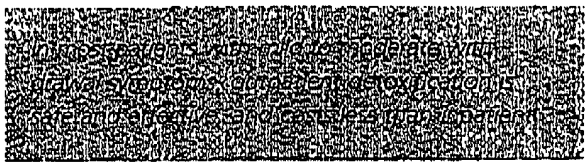
Orientation and clouding of sensorium. Ask "What day is this? Where are you? Who am I?"
Observation:
0—Oriented and can do serial additions
1—Cannot do serial additions or is uncertain about date
2—Date disorientation by no more than two calendar days
3—Date disorientation by more than two calendar days
4—Disoriented for place and/or person

Total score: _____ (maximum = 67) Rater's initials _____

FIGURE 1. Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale.

Adapted from Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). Br J Addict 1989;84:1353-7.

TABLE 3
Examples of Treatment Regimens for Alcohol Withdrawal



istered at specific intervals, and additional doses of the medication are given as needed based on the severity of the withdrawal symptoms. In a symptom-triggered regimen, medication is given only when the CIWA-Ar score is higher than 8 points.

Symptom-triggered regimens have been shown to result in the administration of less total medication and to require a shorter duration of treatment.[11,12] In one randomized, double-blind controlled trial,[11] patients in the symptom-triggered group received an average of 100 mg of chlordiazepoxide, whereas patients in the fixed-schedule group received an average of 425 mg. The median duration of treatment in the symptom-triggered group was nine hours, compared with 68 hours in the fixed-schedule group. Patients were excluded from the study if they had concurrent medical or psychiatric illness requiring hospitalization or seizures from any cause.[11]

Another trial[12] yielded similar results, with patients in the fixed-schedule group receiving an average of 231.4 mg of oxazepam and those in the symptom-triggered group receiving an average of 37.5 mg. Of the patients in the symptom-triggered group, 61 percent did not receive any oxazepam. This trial excluded persons with major psychiatric, cognitive, or medical comorbidities.

The use of symptom-triggered therapy requires training of the clinical staff. If this training has not been provided, fixed-schedule pharmacotherapy should be used.[10]

Choice of Treatment Setting

In most patients with mild to moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than inpatient treatment.[4,13-15] However, certain patients should be considered for inpatient treatment regardless of the severity of their symptoms. Relative indications for inpatient alcohol detoxification are as follows: history of severe withdrawal symptoms, history of withdrawal seizures or delirium tremens, multiple previous detoxifications, concomitant psychiatric or medical illness, recent high levels of alcohol consumption, pregnancy, and lack of a reliable support network.[16]

If outpatient treatment is chosen, the patient should be assessed daily. The patient and support person(s) should be instructed about how to take the withdrawal medication, the side effects of the medication, the expected withdrawal symptoms, and what to do if symptoms worsen.[6,17] Small quantities of the withdrawal medication should be prescribed at each visit; thiamine and a multivitamin also should be prescribed. Because close monitoring is not

available in ambulatory treatment, a fixed-schedule regimen should be used.

Pharmacologic Treatment of Withdrawal

Benzodiazepines

Pharmacologic treatment of alcohol withdrawal syndrome involves the use of medications that are cross-tolerant with alcohol. Benzodiazepines have been shown to be safe and effective, particularly for preventing or treating seizures and delirium, and are the preferred agents for treating the symptoms of alcohol withdrawal syndrome.[10]

The choice of agent is based on pharmacokinetics. Diazepam (Valium) and chlordiazepoxide (Librium) are long-acting agents that have been shown to be excellent in treating alcohol withdrawal symptoms. Because of the long half-life of these medications, withdrawal is smoother, and rebound withdrawal symptoms are less likely to occur. Lorazepam (Ativan) and oxazepam (Serax) are intermediate-acting medications with excellent records of efficacy. Treatment with these agents may be preferable in patients who metabolize medications less effectively, particularly the elderly and those with liver failure. Lorazepam is the only benzodiazepine with predictable intramuscular absorption (if intramuscular administration is necessary).

Rarely, it is necessary to use extremely high dosages of benzodiazepines to control the symptoms of alcohol withdrawal. Dosages of diazepam as high as 2,000 mg per day have been administered.[18] Because clinicians often are reluctant to administer exceptionally high dosages, undertreatment of alcohol withdrawal is a common problem.

One randomized controlled trial (RCT)[19] affirmed previous findings that carbamazepine is an effective alternative to benzodiazepines in the treatment of alcohol withdrawal syndrome in patients with mild to moderate symptoms. Patients in the study received 800 mg of carbamazepine on the first day, with the dosage tapered to 200 mg by the fifth day. Carbamazepine (Tegretol) also appears to decrease the craving for alcohol after withdrawal. It is not sedating and has little potential for abuse. Although carbamazepine is used extensively in Europe, its use in the United States has been limited by lack of sufficient evidence that it prevents seizures and delirium.

Adjunctive Agents

Several medications may be helpful adjuncts to benzodiazepines in the treatment of alcohol withdrawal syndrome. However, these medications should not be used as monotherapy.

Haloperidol (Haldol) can be used to treat agitation and hallucinations, although it can lower the seizure threshold. The use of atenolol (Tenormin) in conjunction with oxazepam has been shown to improve vital signs more quickly and to reduce alcohol craving more effectively than the use of oxazepam alone.[20]

Adjunctive treatment with a beta blocker should be considered in patients with coronary artery disease, who may not tolerate the strain that alcohol withdrawal can place on the cardiovascular system. Clonidine (Catapres) also has been shown to improve the autonomic symptoms of withdrawal.[10] Although phenytoin (Dilantin) does not treat withdrawal seizures, it is an appropriate adjunct in patients with an underlying seizure disorder.

Patient Follow-Up

Treatment of alcohol withdrawal syndrome should be followed by treatment for alcohol dependence. Treatment of withdrawal alone does not address the underlying disease of addiction and therefore offers little hope for long-term abstinence.

In the outpatient setting, brief interventions are helpful in patients with alcohol abuse,[21] but more intense interventions are required in patients with alcohol dependence. The anticonvulsant topiramate (Topamax) has been shown to be an effective adjunctive medication to decrease alcohol consumption and increase abstinence in alcohol-dependent patients.[22]

Some patients achieve dramatic results by joining 12-step groups such as Alcoholics Anonymous and Narcotics Anonymous. Other patients benefit from stays in comprehensive treatment facilities, which offer a combination of a 12-step model, cognitive-behavior therapy, and family therapy. The treatment of alcohol withdrawal syndrome should be supplemented by an individualized, comprehensive treatment program, or at least as many elements of such a program as the patient can tolerate

Strength of Recommendations

Key clinical recommendation	*Strength of recommendation*	*References*
The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale is a validated 10-item assessment tool that can be used to quantify the severity of alcohol withdrawal syndrome, and to monitor and medicate patients going through withdrawal.	A	7,8
Symptom-triggered regimens have been shown to result in the administration of less total medication and to require a shorter duration of treatment.	A	11, 12
In most patients with mild to moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than inpatient treatment.	A	4, 13, 14, 15
Benzodiazepines have been shown to be safe and effective, particularly for preventing or treating seizures and delirium, and are the preferred agents for treating the symptoms of alcohol withdrawal syndrome.	A	10

and afford.

Future Directions

Several medications have shown early promise in the treatment of alcohol withdrawal. In one case report[23] involving five patients, a single 10-mg dose of baclofen resulted in relief of severe withdrawal symptoms. In a preliminary RCT,[24] baclofen also reduced craving in alcohol-dependent patients.

Gabapentin, which is structurally similar to GABA, has been effective in the treatment of alcohol withdrawal in small studies.[25,26] The low toxicity of gabapentin makes it a promising agent. In another study,[27] the anticonvulsant agent vigabatrin, which irreversibly blocks GABA transaminase, improved withdrawal symptoms after only three days of treatment.

Prevention

Early identification of problem drinking allows prevention or treatment of complications, including severe withdrawal. The U.S. Preventive Services Task Force[28] recommends screening patients for problem drinking through a careful history or standardized screening questionnaire. Patients undergoing preoperative evaluation also should be screened, because alcohol withdrawal can complicate recovery from surgery.[29] Elective surgery should be postponed until the dependent patient has not had alcohol for seven to 10 days.

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